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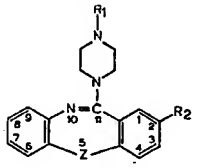
(54) BASICALLY SUBSTITUTED DIBENZOXAZEPINES, DIBENZOTHIAZEPINES AND DIBENZODIAZEPINES

(71) We, DR. A. WANDER S.A., a body corporate organised under the laws of Switzerland of Monbijoustrasse 1115, 3001 Berne, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

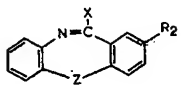
This invention is generally concerned with new heterocyclic compounds. According to the invention there are provided 11-Basically substituted dibenz[b,f]-1,4-oxazepines, dibenzo[b,f]-1,4-thiazepines and dibenzo[b,e]-1,4-diazepines of the formula:



(I)

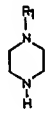
and therapeutically acceptable acid addition salts thereof. In formula I, Z denotes oxygen, sulphur, sulphinyl (—SO—) or imino (—NH—). R_1 represents hydrogen, allyl, alkyl containing not more than 3 carbon atoms, hydroxyalkyl containing not more than 3 carbon atoms, alkoxyalkyl containing not more than 6 carbon atoms or alkanoyloxyalkyl containing not more than 6 carbon atoms. R_2 represents nitro; amino; aminosulphonyl of the formula $—SO_2NR_3R_4$, wherein R_3 and R_4 are the same or different and represent hydrogen or methyl; alkylsulphinyl of the formula $—SOR_5$ in which R_5 denotes alkyl with not more than 3 carbon atoms; or alkylsulphonyl of the formula $—SO_2R_5$ in which R_5 denotes alkyl with not more than 3 carbon atoms.

Compounds of formula I are obtained when a compound of the formula:



(II)

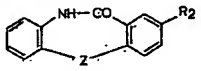
wherein Z and R_2 have the meanings defined above and X denotes a halogen atom or a sulfhydryl, alkoxy, alkylthio, *p*-nitrobenzylthio or tosyl group is reacted with piperazine or a piperazine derivative, respectively, of the formula:



(III),

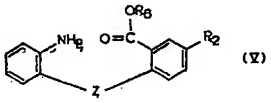
wherein R_1 has the above-mentioned meaning.

Certain of the starting materials of the formula II are obtained by converting lactams of the formula:



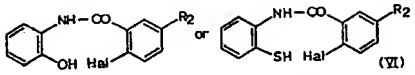
(IV)

wherein Z and R_2 have the meanings given above, into the thiolactams which may be followed by alkylation, or by reaction of the lactams with a halogenating agent such as phosphorus oxychloride or phosphorus pentachloride, most suitably in the presence of a catalytic amount of dimethylaniline or dimethylformamide. Lactams of formula IV are themselves obtained by ring closure of compounds of the formula:



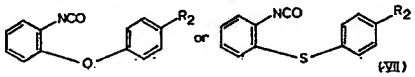
(V)

wherein Z and R_2 have the above-mentioned meanings and R_6 denotes hydrogen or a lower alkyl group containing from 1 to 3 carbon atoms. For products wherein Z represents —O— or —S—, lactams of formula IV may also be obtained by ring closure of compounds of the formula:



(VI)

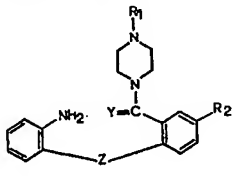
wherein Hal stands for halogen, or of isocyanates of the formula:



(VII)

Lactams of formula IV in which R_2 represents amino are most suitably obtained by reduction of the corresponding nitrolactams.

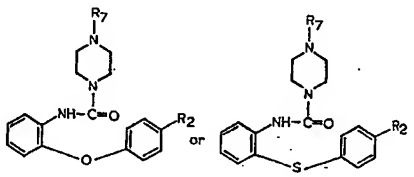
Compounds of formula I may further be obtained by ring closure through intromolecular condensation of acid amides or acid thioamides of the formula:



(VIII),

wherein Z, R_1 and R_2 have the above-mentioned meanings and Y represents oxygen or sulphur. A purely thermal condensation rarely succeeds with the acid amides but rather with the thioamides which are, for example, obtained from the acid amides by treatment with phosphorus pentasulphide and need not be isolated before the following condensation. Especially in the case of the acid amides it is desirable to perform the ring closure in the presence of condensing agents, such as for example phosphorus pentachloride, phosphorus oxychloride, phosgene and polyphosphoric acid. It is assumed that the ring closure proceeds by way of intermediate steps such as imidochlorides, amidochlorides, imidophosphates, amidophosphates or salt-like derivatives thereof, which, in general, are not isolatable. The condensation of the thioamides is favoured by the presence of mercury (II) salts or by intermediate formation of imidothioethers. Heating and, if required, the use of a suitable inert solvent, are desirable, and when using phosphorus oxychloride and phosphorus pentachloride, addition of catalytic amounts of dimethylformamide or dimethylaniline.

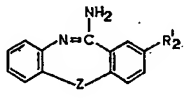
11-Basically substituted dibenz[b,f]-1,4-oxazepines and dibenzo[b,f]-1,4-thiazepines (formula I; Z = —O— or —S—) can also be obtained by dehydration of urea derivatives of the formula:



(IIX),

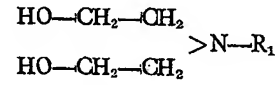
wherein R_2 has the above-mentioned meaning and R_7 means R_1 or denotes a removable group, especially a hydrolytically removable group. The ring closure is preferably carried out by heating in the presence of dehydrating agents such as for example zinc chloride, aluminium chloride, stannic chloride, phosphoric acid and polyphosphoric acid, especially phosphorus oxychloride or phosphorus oxychloride and phosphorus pentoxide, if desired in an inert solvent of suitable boiling point such as for example benzene or toluene. According to the chosen reaction conditions the starting materials of formula IX with a hydrolytically removable group R_7, e.g. carbalkoxy, especially carbethoxy, are cyclized directly to the 11-(1-piperazinyl) compounds by hydrolysis of the removable group. Other removable groups can be split off after ring closure in a way known *per se* e.g. by hydrogenolysis.

As long as R_2 does not denote amino, the products (I) can also be obtained when amidines of the formula:



(X),

wherein Z has the above-mentioned meaning and R'_2 represents R_2 with exclusion of amino, are treated with a reactive ester of an alcohol of the formula:



(XI),

wherein R_1 has the above-mentioned meaning. The reaction is carried out following or by simultaneous treatment with a basic catalyst or metallization agent such as sodamide, lithium amide, sodium hydride, butyl lithium, phenyl sodium, sodium ethylate or potassium-t-butoxide. Suitable esters are those of inorganic or organic acids, e.g. hydrohalic acid, sulphonic acid or carbonic acid esters. The required amidines X are in turn obtained by treating compounds of formula III with ammonia.

On the other hand, compounds of formula I, wherein R_2 is amino, may be obtained by reduction of the corresponding nitro compounds. The reduction is most suitably carried out by treatment with hydrogen in the presence of a catalyst such as palladium

charcoal or Raney nickel or by treatment with stannous chloride and hydrochloric acid.

Compounds of formula I, wherein Z denotes sulphinyl, are also obtained by oxidation, e.g. with periodates, of the corresponding compounds in which Z represents sulphur.

Compounds of formula I, wherein R_2 represents alkylsulphinyl or alkylsulphonyl, respectively, can also be obtained by mild (e.g. with periodates) or strong (e.g. with hydrogen peroxide or peracetic acid) oxidation of the corresponding alkylthio compounds. Products wherein R_2 represents alkylsulphonyl are also obtainable by strong oxidation of the corresponding alkylsulphinyl compounds. If the oxidation is carried out on the dibenzo[b,f]-1,4-thiazepines (Z=—S—) using mild oxidizing agents the corresponding thiazepine sulphoxides Z=—SO—) are obtained.

Finally, compounds of formula I, wherein R_2 denotes aminosulphonyl of the formula $—SO_2NR_3R_4$, are obtained when the corresponding compounds containing the group $—SO_2X'$ instead of aminosulphonyl, wherein X' is a halogen atom, are reacted with ammonia or an amine of the formula HNR_3R_4, wherein R_3 and R_4 have the above defined meaning. Starting materials containing a sulphochloride group ($—SO_2Cl$) are obtained by diazotization of the corresponding amino compounds followed by the Meerwin reaction.

Compounds of formula I, obtained according to one of the above methods, wherein R_1 represents hydrogen and wherein R_2 is not amino can be converted to such compounds wherein R_1 does not represent hydrogen, e.g. by treatment with reactive esters of alcohols of the formula $R_1—OH$. Hydrohalic acid or toluenesulphonic acid esters are suitable for this purpose. An alkyl group R_1 can also be introduced by the method of reductive alkylation, i.e. by reaction with corresponding aldehydes either with hydrogen in the presence of a catalyst or with a reducing agent such as formic acid. The introduction of a hydroxyalkyl group R_1 can also be carried out by treating with a corresponding alkylene oxide.

Compounds of formula I in which R_1 denotes a hydroxyalkyl group and in which R_2 is not amino can be subsequently treated with an alkanoylating agent to obtained products wherein R_1 represents an alkanoyloxyalkyl group. Alkanoic acid chlorides and anhydrides are especially suitable as alkanoylating agents.

The bases obtained in this manner are in most cases crystallizable or can otherwise be distilled in high vacuum without decomposition and react with inorganic and organic acids such as for example hydrochloric acid, hydrobromic acid, sulphuric acid, nitric acid, phosphoric acid, acetic acid, oxalic acid, maleic acid, succinic acid, tartaric acid and toluene sulphonic acid to form addition salts which are stable in water.

The bases obtained in the described manner and their therapeutically acceptable acid addition salts are new compounds which can be used as active substances in pharmaceuticals or as intermediates for the production of such substances. They produce a favourable effect on the central nervous system and may therefore be used as analgesics, neuroleptics, sedatives and especially as neutroleptic antidepressants, and as antiemetics.

Especially compounds of formula I in which R_2 denotes nitro show the typical behaviour pattern for neutroleptics. This manifests pharmacologically e.g. in a suppression of locomotor activity, a cataleptic and/or an apomorphine antagonising effect in mice or rats, respectively. The most effective compounds in this respect are the compounds 2 - nitro - 11 - (4 - methyl - 1 - piperazinyl) - dibenz[b,f] - 1,4 - oxazepine and 2 - nitro - 11 - (4 - methyl - 1 - piperazinyl) - dibenzo[b,f] - 1,4 - thiazepine, obtained according to Example 1 or 2, respectively, as well as their therapeutically acceptable acid addition salts.

Other compounds, especially those with 11 - (1 - piperazinyl) residues show simultaneously the behaviour pattern for neuroleptics and antidepressants whereby the antidepressant action is shown pharmacologically by a tetrabenazine antagonism observed in rats. Especially active in this respect are the compounds 2 - nitro - 11 - (1 - piperazinyl) - dibenz[b,f] - 1,4 - oxazepine and 2 - nitro - 11 - (1 - piperazinyl) - dibenzo[b,f] - 1,4 - thiazepine obtained according to Example 18 or 20, respectively, and their therapeutically acceptable acid addition salts.

Compounds of formula I in which R_2 represents aminosulphonyl or alkylsulphonyl exhibit a marked antiemetic activity. This is shown pharmacologically by a strong apomorphine antagonising effect in dogs and rats as well as a comparatively weak cataleptic and locomotor activity suppressing effect. Pronounced antiemetic activity is shown by 2 - dimethylaminosulphonyl - 11 - (4 - methyl - 1 - piperazinyl) - dibenzo[b,f] - 1,4 - thiazepine, 2 - dimethylaminosulphonyl - 11 - (4 - methyl - 1 - piperazinyl) - dibenz[b,f] - 1,4 - oxazepine, 2 - methylsulphonyl - 11 - (4 - methyl - 1 - piperazinyl) -

dibenz[b,f] - 1,4 - oxazepine and 2 - methylsulphonyl - 11 - (4 - methyl - 1 - piperazinyl) - dibenzo[b,f] - 1,4 - thiazepine obtained according to Examples 3, 4, 5 or 26, respectively, and their therapeutically acceptable acid addition salts.

The compounds of this invention can be administered in the form of pharmaceutical preparations containing, besides the active substance, organic or inorganic solid or liquid carriers suitable for enteral or parenteral administration. The pharmaceutical preparations may be, for example, in the form of tablets, dragees, or solutions for injection, one dosage unit containing from 10 to 25 mg of active substance, depending on its nature, on the route of administration and on the physician's prescription, the effective daily dose amounting to from 5 to 400 mg of active substance.

The following Examples illustrate the invention:—

Example 1

4.9 g of 2 - Nitro - 10,11 - dihydro - 11 - oxo - dibenz[b,f] - 1,4 - oxazepine (m.p. 263°C) and 2 ml of N,N - dimethylaniline are heated in 60 ml of phosphorus oxychloride at reflux for 4 hours. The reaction mixture is then evaporated *in vacuo* to remove the excess phosphorus oxychloride and the residue is decomposed with ice/water and shaken out immediately with chloroform. The chloroform extracts are washed with dilute hydrochloric acid and water, dried over sodium sulphate and evaporated to dryness *in vacuo*. The crystalline residue consisting of crude 2 - nitro - 11 - chloro - dibenz[b,f] - 1,4 - oxazepine is heated at reflux for 6 hours with 6 ml of N - methylpiperazine in 200 ml of xylene. The organic phase is then shaken out with water and dilute hydrochloric acid. The acid extracts are made alkaline with concentrated soda lye and the base which separates is extracted with chloroform. The chloroform extracts are washed with water, dried over sodium sulphate and evaporated to dryness. The residue is crystallized from chloroform/acetone/petroleum ether and gives 4.7 g. of 2 - nitro - 11 - (4 - methyl - 1 - piperazinyl) - dibenz[b,f] - 1,4 - oxazepine in the form of yellow needles of melting point 192—193°C.

Example 2

2.0 g of 2 - Nitro - 10,11 - dihydro - 11 - oxo - dibenzo[b,f] - 1,4 - thiazepine (m.p. 270—286°C dec.) and 1 ml of N,N - dimethylaniline are refluxed with 15 ml of phosphorus oxychloride for 5 hours after which the reaction mixture is evaporated to dryness *in vacuo*. The residue is treated with xylene, once again evaporated *in vacuo* and then refluxed for 16 hours with 15 ml of N - methylpiperazine and 10 ml of dioxane. After evaporating to dryness *in vacuo*, the residue is distributed between ether and dilute aqueous ammonia solution. The ether phase is washed twice with water and then shaken out with dilute acetic acid. The base is set free from the acid extracts by addition of concentrated ammonia solution and taken up in ether. The ether phase is washed four times with water, dried over sodium sulphate and evaporated. The resinous residue obtained is then dissolved in ether, filtered through aluminium oxide and evaporated. The residue is crystallized from acetone/petroleum ether to give 1.7 g of 2 - nitro - 11 - (4 - methyl - 1 - piperazinyl) - dibenzo[b,f] - 1,4 - thiazepine in the form of yellow matted needles of melting point 141—142°C.

Example 3

4.5 g. of 2 - Dimethylaminosulphonyl - 10,11 - dihydro - 11 - oxodibenzo[b,f] - 1,4 - thiazepine (m.p. 283—284°C) and 1.3 ml of N,N-dimethylaniline are refluxed in 40 ml of phosphorus oxychloride for 4.5 hours. The excess phosphorus oxychloride is then distilled off *in vacuo* and the residue is dissolved in xylene. The xylene solution is poured onto ice/water, shaken out twice with dilute hydrochloric acid and once with water, dried over sodium sulphate and then concentrated to 100 ml *in vacuo*. 8 ml of N - methylpiperazine are added and the reaction mixture is refluxed for 4 hours and then treated with dilute soda lye and water. The xylene phase is separated and shaken out with dilute hydrochloric acid. The acid extracts are made alkaline with concentrated ammonia solution and the base which separates is extracted with chloroform. After drying over sodium sulphate the chloroform extracts are evaporated *in vacuo*. The residue is crystallized from acetone/petroleum ether whereby 4.9 g of 2 - dimethylaminosulphonyl - 11 - (4 - methyl - 1 - piperazinyl) - dibenzo[b,f] - 1,4 - thiazepine are obtained in the form of slightly yellow needles of melting point 192—193°C.

EXAMPLE 4

11.8 g of 2 - Dimethylaminosulphonyl - 10,11 - dihydro - 11 - oxodibenz[b,f] - 1,4 - oxazepine (m.p. 243—245°C) and 0.6 ml of N,N - dimethylaniline are refluxed in 20 ml of phosphorus oxychloride for 4 hours. The excess phosphorus oxychloride is removed completely *in vacuo* and the residue dissolved in xylene and poured onto ice/water. The xylene solution is shaken out twice with dilute hydrochloric acid and once with water, then dried over sodium sulphate and concentrated to 50 ml *in vacuo*. 3 ml of N - methylpiperazine are added and the reaction mixture is refluxed for 4 hours and then treated with dilute soda lye and water. The xylene phase is separated and shaken out with dilute hydrochloric acid. The acid extracts are made alkaline with concentrated ammonia solution and the base which separates is extracted with chloroform. The chloroform extracts are dried over sodium sulphate and evaporated *in vacuo*. The residue is crystallized from ether/petroleum ether whereby 1.8 g of 2 - dimethylaminosulphonyl - 11 - (4 - methyl - 1 - piperazinyl) - dibenz[b,f] - 1,4 - oxazepine of melting point 149—150°C are obtained.

EXAMPLE 5

5 g of 2 - Methylsulphonyl - 10,11 - dihydro - 11 - oxo - dibenz[b,f] - 1,4 - oxazepine (m.p. 242—244°C) and 11.8 ml of N,N - dimethylaniline are refluxed in 50 ml of phosphorus oxychloride for 5 hours after which the reaction mixture is evaporated to dryness *in vacuo*. The residue is treated with xylene, once again evaporated and then dissolved in xylene and poured onto ice. The aqueous phase is shaken out three times with xylene. The combined xylene extracts are washed with dilute hydrochloric acid, water and aqueous sodium chloride solution, dried over sodium sulphate, treated with active charcoal and filtered through a small amount of aluminium oxide. The filtrate is concentrated and then refluxed with 12 ml of N-methylpiperazine for 6 hours. The reaction mixture is treated with water and concentrated soda lye and shaken out twice with ether. The ether extracts are washed several times with water and then shaken out with dilute hydrochloric acid. The acid extracts are made alkaline and extracted twice with ether. The ether phase is washed with water and aqueous sodium chloride solution, dried over sodium sulphate, treated with active charcoal and filtered through a small amount of aluminium oxide. The filtrate is concentrated and treated with petroleum ether. The crystals which precipitate are dissolved in acetone and, after concentrating, recrystallized by addition of ether/petroleum ether. 5.8 g of 2 - methylsulphonyl - 11 - (4 - methyl - 1 - piperazinyl) - dibenz[b,f] - 1,4 - oxazepine in the form of slightly yellow needles of melting point 178—179°C are obtained.

EXAMPLE 6

3.72 g of 2 - Amino - 2' - (4'' - methyl - 1'' - piperazinyl - carbonyl) - 4' - nitro - diphenylsulphide (m.p. 184—187°C) and 1 ml of N,N - dimethylaniline are refluxed for 3 hours in 20 ml of phosphorus oxychloride after which the reaction mixture is evaporated to dryness. The residue is treated with xylene, once again evaporated and then partitioned between benzene and dilute hydrochloric acid. The base is set free from the acid extracts with concentrated ammonia solution and taken up in benzene. The benzene solution its exhaustively extracted with dilute acetic acid and the acetic acid extracts are treated with active charcoal. The basic fraction is set free, under ice-cooling, with concentrated ammonia solution and taken up in chloroform. The chloroform extracts are washed with water, dried over sodium sulphate and evaporated. The residue is dissolved in ether and filtered through aluminium oxide. The residue obtained after evaporation of the solvent is systematically crystallized from acetone/ether/petroleum ether. The first fraction to crystallize is 0.6 g of starting material. 0.72 g of 2 - nitro - 11 - (4 - methyl - 1 - piperazinyl) - dibenzo[b,] - 1,4 - thiazepine of melting point 138—141°C is obtained from the more soluble portion. This compound is identical to the product obtained according to Example 2.

EXAMPLE 7

3 g of 2 - (4'' - Methyl - 1'' - piperazinyl - carbonylamino) - 4' - methylsulphonyl - diphenyloxide (m.p. 145—146°C) and a mixture of 2 g of phosphorus pentoxide and 10 ml of phosphorus oxychloride are refluxed for 24 hours. The excess phosphorus oxychloride is then distilled off *in vacuo* and the residue decomposed with ice/water. The solution obtained is made alkaline with concentrated soda lye and shaken out with ether. The ether extracts are washed with water and shaken out thoroughly with dilute hydrochloric acid. The acid extracts are made alkaline with concentrated soda lye and shaken out with chloroform. The chloroform extracts are washed with water, dried over sodium sulphate and evaporated to dryness *in vacuo*. The residue is crystal-

lized from acetone/petroleum ether and gives 1.5 g of 2 - methylsulphonyl - 11 - (4 - methyl - 1 - piperazinyl) - dibenz[b,f] - 1,4 - oxazepine of melting point 178—179°C identical to the product obtained according to Example 5.

EXAMPLE 8

7.9 g of 2 - Nitro - 11 - amino - dibenz[b,f] - 1,4 - oxazepine (m.p. 238—240°C) and potassium-t-butoxide (from 4.0 g of potassium) are stirred together in 40 ml of dimethylsulphoxide for 30 minutes. After addition of 7.5 g of bis - (β - chloroethyl)-methylamine hydrochloride, 1.3 g of potassium iodide and a further 20 ml of dimethylsulphoxide the mixture is stirred for a further 14 hours at 80°C. The reaction mixture is then partitioned between benzene and a large volume of water. The benzene layer is washed with water, then exhaustively extracted with dilute acetic acid. The acetic acid extracts are treated with active charcoal, cooled with ice and made alkaline with concentrated soda lye. The base which is set free is taken up in chloroform. The chloroform solution is washed with water, dried with sodium sulphate and evaporated. The residue is dissolved in benzene and filtered through aluminium oxide. After concentration and dilution with petroleum ether, crystals precipitate which are then recrystallized from chloroform/acetone/petroleum ether to give 4.3 g of 2 - nitro - 11 - (4 - methyl - 1 - piperazinyl) - dibenz[b,f] - 1,4 - oxazepine of melting point 192—194°C which is identical to the product obtained according to Example 1.

EXAMPLE 9

15.2 g of 2 - Nitro - 11 - (4 - methyl - 1 - piperazinyl - dibenz[b,f] - 1,4 - oxazepine obtained according to Example 1 are hydrogenated with hydrogen in the presence of 1 g of 5% palladium-charcoal in 450 ml of methanol at normal pressure. After take-up of 3.05 l of hydrogen, the hydrogenation is discontinued and the reaction mixture filtered to remove the catalyst. The filtrate is evaporated *in vacuo* and the residue taken up in chloroform, filtered through aluminium oxide and concentrated. On addition of petroleum ether, crystals are formed which are separated and recrystallized from chloroform/ether/petroleum ether. 14.1 g of 2 - amino - 11 - (4 - methyl - 1 - piperazinyl) - dibenz[b,f] - 1,4 - oxazepine of melting point 153—156°C are obtained.

EXAMPLE 10

11.5 g of 2 - Nitro - 11 - (4 - methyl - 1 - piperazinyl) - dibenzo[b,f] - 1,4 - thiazepine obtained according to Example 2 are mixed with 24.5 g of stannous chloride and while stirring and cooling with ice, treated dropwise with dilute hydrochloric acid (238 ml of concentrated hydrochloric acid and 100 ml of water). The reaction mixture becomes lighter in colour and a white precipitate is formed. After the addition is complete, the reaction mixture is stirred for a further 20 minutes while cooling, then for 15 minutes at 40°C. The reaction mixture is thereupon made strongly alkaline with concentrated soda lye and the precipitate taken up in ether. The ether phase is exhaustively shaken out with dilute acetic acid and the base liberated from the acetic acid extracts by addition of concentrated ammonia solution and taken up in ether. The ether phase is washed with water, dried over sodium sulphate and evaporated. The residue is dissolved in ether, filtered through aluminium oxide and evaporated. After crystallization of the residue from ether/petroleum ether, 10.05 g of 2 - amino - 11 - (4 - methyl - 1 - piperazinyl) - dibenzo[b,f] - 1,4 - thiazepine are obtained as colourless prisms of melting point 165—167°C.

EXAMPLE 11

A solution of 3.4 g of sodium metaperiodate in 40 ml of water is added in one lot a solution of 5.3 g of 2 - nitro - 11 - (4 - methyl - 1 - piperazinyl) - dibenzo[b,f] - 1,4 - thiazepine, obtained according to Example 2, while stirring under ice-cooling. The reaction mixture is then stirred at room temperature for 5 hours and left to stand overnight. After diluting with water and treating with active charcoal, the basic fraction is set free under ice-cooling with concentrated soda lye and taken up in benzene. The benzene solution is washed with water, dried over sodium sulphate and concentrated. The solution is filtered through aluminium oxide and evaporated to dryness. The residue is crystallized from acetone and acetone/petroleum ether to give 4.3 g of 2 - nitro - 11 - (4 - methyl - 1 - piperazinyl) - dibenzo[b,f] - 1,4 - thiazepine - 5 - oxide in the form of yellow matted needles of melting point 182—185°C.

EXAMPLE 12

A solution of 3.42 g of sodium metaperiodate in 10 ml of water is given in 3 portions to a stirred solution of 6.24 g of 2 - dimethylaminosulphonyl - 11 - (4 - methyl-1 - piperazinyl) - dibenzo[b,f] - 1,4 - thiazepine obtained according to Example 3, in 40 ml of water and 10 ml of glacial acetic acid at 0°C. A precipitate which appears is brought into solution by adding 20 ml of 2 N acetic acid. The reaction mixture is kept

at room temperature for 24 hours, then made alkaline with concentrated soda lye and shaken out with chloroform. The chloroform extracts are washed with water, dried over sodium sulphate and evaporated to dryness *in vacuo*. The residue is crystallized from acetone/petroleum ether to give 5.9 g of 2 - dimethylaminosulphonyl - 11 - (4 - methyl - 1 - piperazinyl) - dibenzo[b,f] - 1,4 - thiazepine - 5 - oxide of melting point 208—210°C.

EXAMPLE 13

The free base obtained from 6.83 g of 2 - thiomethyl - 11 - (4 - methyl - 1 - piperazinyl) - dibenz[b,f] - 1,4 - oxazepine maleate (m.p. 198—201°C) is dissolved in 40 ml of water and 10 ml of glacial acetic acid. This solution is treated dropwise while stirring at 0°C with a solution of 3.42 g of sodium metaperiodate in 10 ml of water. After the addition is complete, the reaction mixture is left to stand at room temperature for 24 hours, then made alkaline with concentrated soda lye and shaken out with ether. The ether extracts are washed with water and then exhaustively shaken out with dilute hydrochloric acid. The acid extracts are made alkaline with concentrated soda lye and shaken out with chloroform. The chloroform extracts are washed with water, dried over sodium sulphate and evaporated to dryness *in vacuo*. The residue is dissolved in acetone and treated with 1.8 g of maleic acid. After concentration and addition of ether, crystals precipitate which are recrystallized from methanol/acetone/ether to give 6.0 g of 2 - methylsulphinyl - 11 - (4 - methyl - 1 - piperazinyl) - dibenz-[b,f] - 1,4 - oxazepine maleate of melting point 206—207°C.

EXAMPLE 14

A solution of 5.2 g of crude 2 - chlorosulphonyl - 11 - (4 - methyl - 1 - piperazinyl) - dibenz[b,f] - 1,4 - oxazepine, obtained as described below, in 80 ml of chloroform is treated dropwise at room temperature with 50 ml of a 10% dimethylamine solution in toluene. The reaction mixture is stirred for a further 2 hours at room temperature, then for 1 hour at 40°C and finally evaporated to dryness *in vacuo*. The residue is taken up in dilute acetic acid, treated with active charcoal and made alkaline with concentrated ammonia solution. The base which separates is taken up in benzene, the benzene solution washed three times with water, dried over sodium sulphate and evaporated. The residue is taken up in benzene and filtered through basic aluminium oxide. The residue obtained after evaporation of the solvent is crystallized from acetone/petroleum ether to give 3.2 g of 2 - dimethylaminosulphonyl - 11 - (4 - methyl - 1 - piperazinyl) - dibenz[b,f] - 1,4 - oxazepine of melting point 148—150°C which is identical to the product obtained according to Example 4.

2 - Chlorosulphonyl - 11 - (4 - methyl - 1 - piperazinyl) - dibenz[b,f] - 1,4 - oxazepine used as starting material is obtained as follows:

15.4 g of 2 - Amino - 11 - (4 - methyl - 1 - piperazinyl) - dibenz[b,f] - 1,4 - oxazepine (m.p. 153—156°C) are dissolved in 50 ml of glacial acetic acid and 15 ml of 38% hydrochloric acid and diazotized in the usual manner at 0°—5°C with a solution of 3.6 g of sodium nitrite in 6 ml of water. The diazonium solution obtained is added within a few minutes while stirring at 10°C to 40 ml of a 30% solution of sulphur dioxide in glacial acetic acid containing 2 g of cuprous chloride. After the development of nitrogen subsides at room temperature, the reaction mixture is warmed for 15 minutes at 40°C. The reaction mixture is then diluted to 1 l with water and treated with active charcoal. While stirring and cooling carefully, the basic fraction is precipitated with concentrated soda lye and taken up in chloroform. The chloroform extracts are washed once with dilute soda lye and once with water, dried over sodium sulphate and evaporated. Crude 2 - chlorosulphonyl - 11 - (4 - methyl - 1 - piperazinyl) - dibenz-[b,f] - 1,4 - oxazepine is obtained as residue.

EXAMPLE 15

5.4 g of 2 - Dimethylaminosulphonyl - 11 - (1 - piperazinyl) - dibenz[b,f] - 1,4 - oxazepine obtained according to Example 42 are dissolved in 50 ml of acetone and treated with 1 g of anhydrous potassium carbonate and 2.24 g of ethyl iodide in 20 ml of acetone and refluxed for 3 hours while stirring. The reaction mixture is then evaporated *in vacuo* and the residue distributed between dilute soda lye and ether. The ether extracts are washed with water and exhaustively shaken out with dilute aqueous hydrochloric acid. The acid extracts are made alkaline with concentrated soda lye and shaken out with chloroform. The chloroform extracts are washed with water, dried over sodium sulphate and evaporated to dryness *in vacuo*. The residue is crystallized from acetone/petroleum ether to give 4.9 g of 2 - dimethylaminosulphonyl - 11 - (4 - ethyl - 1 - piperazinyl) - dibenz[b,f] - 1,4 - oxazepine of melting point 160—161°C.

EXAMPLE 16

4.63 g of the same starting material as in Example 15 are dissolved in 80 ml of isopropanol and treated with 1.6 g of anhydrous potassium carbonate, then, while stirring and heating, treated dropwise with 3 g of β - methoxyethyl - *p* - toluene sulphonic acid ester in 110 ml of isopropanol. After the addition is complete, the mixture is refluxed for 1.5 hours, then evaporated *in vacuo*. The residue is partitioned between dilute soda lye and ether and the ether extracts exhaustively shaken out with dilute hydrochloric acid. The acid extracts are made alkaline with concentrated soda lye and shaken out with ether. The ether extracts are washed with water, dried over sodium sulphate and evaporated *in vacuo*. The oily residue is dissolved in warm acetone together with 1.2 g of maleic acid and crystallized by addition of ether. 4.9 g of 2 - dimethylaminosulphonyl - 11 - (4 - β - methoxyethyl - 1 - piperazinyl) - dibenz[b,f] - 1,4 - oxazepine maleate of melting point 124—140°C (decomposition) are obtained.

EXAMPLE 17

4 g of 2 - Dimethylaminosulphonyl - 11 - (4 - β - hydroxyethyl - 1 - piperazinyl)-dibenz[b,f] - 1,4 - oxazepine obtained according to Example 39 are mixed with 30 ml of absolute pyridine and 15 ml of acetic anhydride, the mixture left to stand for one hour at room temperature and then warmed for a short time on the steam bath. The reaction mixture is evaporated *in vacuo* and the residue diluted with water. The basic fraction is precipitated in the cold with concentrated soda lye and exhaustively extracted with ether. The ether phase is washed with water, dried over sodium sulphate and evaporated. The residue is dissolved in acetone and treated with 1.8 g of maleic acid. After concentration of the solution and addition of ether, crystals precipitate which are recrystallized from acetone/ether to give 3 g of 2 - dimethylaminosulphonyl - 11 - (4 - β - acetoxyethyl - 1 - piperazinyl) - dibenz[b,f] - 1,4 - oxazepine maleate of melting point 155—158°C.

Further products corresponding to formula I given in the following table are obtained by analogous procedures to those given above. In the table Z, R_1 and R_2 have the above defined meaning. In the column on the right hand side ac means acetone, e = ether, ch = chloroform, me = methanol and pe = petroleum ether.

TABLE

Example	Z	R_1	R_2	Melting Point
18	O	H	$-NO_2$	base: 190—192°C (from ac/pe)
19	O	$-CH_2-CH_2-OH$	$-NO_2$	maleate: 155—156°C (from me/ac)
20	S	H	$-NO_2$	base: 153—155°C (from ac/pe)
21	S	$-CH_2-CH_2-OH$	$-NO_2$	base: 130—134°C (from ac/pe)
22	S	H	$-SO_2N(CH_3)_2$	base: 186—188°C (from ch/e)
23	NH	$-CH_3$	$-SO_2N(CH_3)_2$	base: 193—195°C (from ac/pe)
24	O	H	$-SO_2CH_3$	base: 189—191°C (from ac/e/pe)
25	O	H	$-NH_2$	base: 181—183°C (from ethyl acetate/e)
26	S	$-CH_3$	$-SO_2CH_3$	base: 219—223°C (from ac/pe)
27	S	H	$-SO_2CH_3$	base: 180—183°C (from ch/pe)
28	S	$-CH_3$	$-SO_2C_2H_5$	base: 169—170°C (from ch/pe)
29	S	H	$-SO_2C_2H_5$	maleate: 180—185°C. (from me/ac/e)
30	O	$-CH_3$	$-SO_2C_2H_5$	base: 196—197°C (from ch/pe)

Example	Z	R_1	R_2	Melting Point
31	NH	$-CH_3$	$-NO_2$	base: 110—112°C (from ac/pe)
32	NH	H	$-SO_2N(CH_3)_2$	base: 147—150°C (from ac/pe)
33	NH	$-CH_3$	$-SO_2CH_3$	dihydrobromide: 225—230°C (dec.; from me/ethyl acetate)
34	NH	H	$-SO_2CH_3$	dihydrobromide: 233—248°C from me/ethyl acetate)
35	S	H	$-SO_2NHCH_3$	base: 218—222°C (from ac/pe)
36	S	$-CH_3$	$-SO_2NHCH_3$	base: 168—170°C (from(ac/pe)
37	O	H	$-SO_2C_2H_5$	base: 130—133°C (from ac/pe)
38	O	$-CH_2-CH_2-OCH_3$	$-NO_2$	base: 102—104°C (from e/pe)
39	O	$-CH_2-CH_2-OH$	$-SO_2N(CH_3)_2$	base: 164—166°C (from ac/e/pe)
40	SO	H	$-NO_2$	base: 174—176°C (from ac/pe)
41	O	$-CH_2-CH=CH_2$	$-SO_2N(CH_3)_2$	base: 150—151°C (from ac/pe)
42	O	H	$-SO_2N(CH_3)_2$	base: 181—182°C (from ac/pe)

Production of tablets

For the manufacture of tablets, the products of this invention can be mixed with lactose and granulated with water, 0.5% sodium alginate or 1% gelatine solution. The dried granulate is compressed into tablets in the presence of about 5% of talcum, 5% of corn starch and 0.1% of magnesium stearate. In this way, there are obtained, e.g. tablets of the following composition:

A)

2-Nitro-11-(4-methyl-1-piperazinyl)-dibenz[b,f]-1,4-oxazepine	25 mg
Lactose	115 mg
Corn starch	7.5 mg
Talcum	7.5 mg
Magnesium stearate	0.15 mg

These 155 mg tablets, which are provided with a crack-line, can be administered orally in a dosage of one half to two tablets two to four times per day in the treatment of subjects suffering from any form of schizophrenia, any form of mania, severe psychotic and non-psychotic states of excitement, chorea, athetosis, and extrapyramidal movement disorders.

B)

2-Nitro-11-(1-piperazinyl)-dibenz[b,f]-1,4-oxazepine	20 mg
Lactose	120 mg
Corn starch	7.5 mg
Talcum	7.5 mg
Magnesium stearate	0.15 mg

These 155 mg tablets, which are provided with a crack-line, can be administered orally in the dosage of one half to two tablets two to five times, in some cases up to 5 times 4 tablets per day in the treatment of subjects suffering from states of mental depression and especially agitated forms of depression.

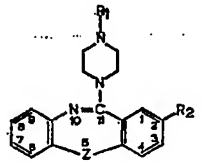
C)

2-Dimethylaminosulphonyl-11-(4-methyl-1-piperazinyl)-dibenz[b,f]-1,4-oxazepine	10 mg
Lactose	70 mg
Corn starch	5 mg
Talcum	5 mg
Magnesium stearate	0.1 mg

These 90 mg tablets, which are provided with a crack-line, can be administered orally in a dosage of one half to two tablets one to three times per day in the treatment of subjects suffering from nausea and vomiting following operations or ray treatment or due to stomach or metabolism disorders, intoxications, drug incompatibility, pressure on the brain or pregnancy. These tablets may also be used prophylactically against post operative vomiting.

WHAT WE CLAIM IS:—

1. 11-Basically substituted dibenz[b,f]-1,4-oxazepines, dibenzo[b,f]-1,4-thiazepines and dibenzo[b,e]-1,4-diazepines of the formula:



wherein Z represents an oxygen or sulphur atom or a sulphinyl or imino group; R_1 represents a hydrogen atom, an allyl radical, an alkyl radical containing not more than 3 carbon atoms, a hydroxyalkyl radical containing not more than 3 carbon atoms, an

alkoxyalkyl radical containing not more than 6 carbon atoms or an alkanoyloxyalkyl radical containing not more than 6 carbon atoms; and R_2 is a nitro or an amino group, an aminosulphonyl group of the formula $—SO_2NR_3R_4$ wherein R_3 and R_4, which may be the same or different, are hydrogen atoms or methyl groups, or R_2 represents an alkylsulphinyl group of the formula $—SOR_5$ wherein R_5 denotes an alkyl radical with not more than 3 carbon atoms, or an alkylsulphonyl group of the formula $—SO_2R_5$ wherein R_5 denotes an alkyl radical with not more than 3 carbon atoms, and therapeutically acceptable acid addition salts thereof.

2. 2 - Nitro - 11 - (4 - methyl - 1 - piperazinyl) - dibenz[b,f] - 1,4 - oxazepine and its therapeutically acceptable acid addition salts.

3. 2 - Nitro - 11 - (4 - methyl - 1 - piperazinyl) - dibenzo[b,] - 1,4 - thiazepine and its therapeutically acceptable acid addition salts.

4. 2 - Nitro - 11 - (piperazinyl) - dibenz[b,f] - 1,4 - oxazepine and its therapeutically acceptable acid addition salts.

5. 2 - Nitro - 11 - (1 - piperazinyl - dibenzo[b,f] - 1,4 - thiazepine and its therapeutically acceptable acid addition salts.

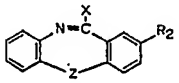
6. 2 - Dimethylaminosulphonyl - 11 - (4 - methyl - 1 - piperazinyl) - dibenzo-[b,f] - 1,4 - thiazepine and its therapeutically acceptable acid addition salts.

7. 2 - Dimethylaminosulphonyl - 11 - (4 - methyl - 1 - piperazinyl) - dibenz-[b,f] - 1,4 - oxazepine and its therapeutically acceptable acid addition salts.

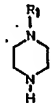
8. 2 - Methylsulphonyl - 11 - (4 - methyl - 1 - piperazinyl) - dibenz[b,f] - 1,4 - oxazepine and its therapeutically acceptable acid addition salts.

9. 2 - Methylsulphonyl - 11 - (4 - methyl - 1 - piperazinyl) - dibenzo[b,f] - 1, 4- thiazepine and its therapeutically acceptable acid addition salts.

10. A process for the preparation of 11-basically substituted dibenz[b,f] - 1,4 - oxazepines, dibenzo[b,f] - 1,4 - thiazepines and dibenzo[b,e] - 1,4 - diazepines of the formula given in claim 1 in which a compound of the formula:

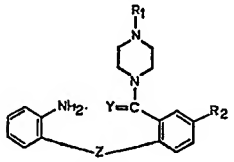


wherein Z and R_2 have the meanings given in claim 1 and X denotes a halogen atom or a sulphydryl, alkoxy, alkylthio, f-nitrobenzylthio or tosyl group, is reacted with piperazine or a piperazine derivative of the formula:



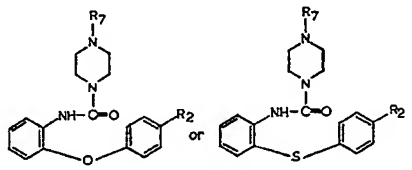
wherein R_1 has the meaning given in claim 1.

11. A process for the preparation of 11-basically substituted dibenz[b,f] - 1,4 - oxazepines, dibenzo[b,f] - 1,4 - thiazepines and dibenzo[b,a] - 1,4 - diazepines of the formula given in claim 1 in which an acid amide or thioamide of the formula:



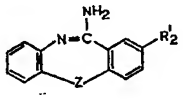
wherein Z, R_1 and R_2 have the meanings given in claim 1 and Y represents an oxygen or sulphur atom, is subjected to intramolecular condensation.

12. A process for the preparation of 11-basically substituted dibenz[b,f] - 1,4 - oxazepines and dibenzo[b,f] - 1,4 - thiazepines of the formula given in claim 11 wherein Z is an oxygen or sulphur atom, in which a urea derivative of the formula:

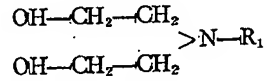


wherein R_2 has the meaning given in claim 1 and R_7 has the same meaning as R_1 or denotes a readily removable group, is subjected to dehydration, if necessary with subsequent splitting off of the removable group.

13. A process for the preparation of 11-basically substituted dibenz[b,f] - 1,4 - oxazepines, dibenz[b,f] - 1,4 - thiazepines and dibenz[b,e] - 1,4 - diazepines of the formula given in claim 1 wherein R_2 is a nitro group or an aminosulphonyl, alkylsulphinyl or alkylsulphonyl group of formulae $-SO_2NR_3R_4$, $-SOR_5$ or $-SO_2R_5$ respectively in which R_3, R_4 and R_5 have the meanings given in claim 1, in which an amidine of the formula:



wherein Z has the meaning given in claim 1 and R'_2 represents a nitro group or an aminosulphonyl, alkylsulphinyl or alkylsulphonyl group of the formulae $-SO_2NR_3R_4$, SOR_5, or SO_2R_5 respectively wherein R_3, R_4, and R_5 have the meanings given in claim 1, is reacted with a reactive ester of an alcohol of the formula:



wherein R_1 has the meaning given in claim 1.

14. A process as claimed in any one of claims 10 to 13 in which, when R_2 is a nitro group, the product is subsequently reduced to give a compound in which R_2 represents an amino group.

15. A process as claimed in any one of claims 10 to 13 in which, in the preparation of a compound of the formula claimed in claim 1 in which R_2 represents an alkylsulphinyl or alkylsulphonyl group a reactant containing a precursor of the group R_2 is used, which precursor is a thioalkyl group of formula SR_5, R_5 having the meaning given in claim 1 which precursor is subsequently oxidised to the alkylsulphinyl or alkylsulphonyl group, or an alkylsulphinyl group which is subsequently oxidised to an alkylsulphonyl group.

16. A process as claimed in any one of claims 10 to 13 in which, in the preparation of a compound of the formula claimed in claim 1 in which R_2 represents an aminosulphonyl group, a reactant containing a precursor of the group R_2 is used, which precursor is a group of formula $-SO_2X'$ wherein X' denotes a halogen atom and is subsequently reacted with ammonia or an amine of the formula HNR_3R_4 wherein R_3 and R_4 have the meanings given in claim 1.

17. A process as claimed in any one of claims 10 to 16 in which, in the preparation of a compound of the formula claimed in claim 1 in which Z represents a sulphinyl group, a compound of said formula in which Z represents a sulphur atom is first prepared and is subsequently oxidised.

18. A process as claimed in any one of claims 10 to 17 in which, in the preparation of a compound of the formula claimed in claim 1, a compound of said formula in which R_1 represents a hydrogen atom and R_2 is not amino is first obtained, and the hydrogen atom is subsequently replaced by an alkyl group, an alkyl radical containing not more than 3 carbon atoms, a hydroxyalkyl radical not containing more than 3 carbon atoms, an alkoxyalkyl radical containing not more than 6 carbon atoms or an alkanoyloxy alkyl radical containing not more than 6 carbon atoms.

19. A process as claimed in claim 18 in which the hydroxyalkyl group R_1 is subsequently alkanoylated.

20. A process as claimed in any one of claims 10 to 19 in which the product is isolated as an acid addition salt.

21. A process as claimed in any one of claims 10 to 19 in which the product is isolated as the free base.

22. A process for the preparation of compounds of the formula given in claim 1 substantially as herein described with reference to Example 1.

23. A process for the preparation of compounds of the formula given in claim 1 substantially as herein described with reference to Examples 2, 18 and 19.

24. A process for the preparation of compounds of the formula given in claim 1 substantially as herein described with reference to Examples 3 and 4.

25. A process for the preparation of compounds of the formula given in claim 1 substantially as herein described with reference to Examples 5, 9, 10, and 20 to 24.

26. A process for the preparation of compounds of the formula given in claim 1 substantially as herein described with reference to Examples 25 to 34.

27. A process for the preparation of compounds of the formula given in claim 1 substantially as herein described with reference to Examples 6 to 8, 11 to 17, and 35 to 42.

28. Dibenzo oxazepines, dibenzo thiazepines and dibenzo diazepines as claimed in claim 1 when produced by the process claimed in any one of claims 10 to 27.

29. Therapeutic compositions comprising a compound as claimed in claim 1 in association with a pharmaceutically acceptable carrier.

30. Compositions as claimed in claim 29 in which one dosage unit contains from 10 to 25 mg of active substance.

31. Therapeutic compositions as claimed in claim 29 substantially as herein described.

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